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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/211,691	GILBERT ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-27 and 33-48* is/are pending in the application.

4a) Of the above claim(s) *13-22 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-12,23-27,33-35 and 37-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *25* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-3, 5-27, 33-48 are currently pending and are present for examination. Claims 1-3, 5-12, 23-27, 33-35, 37-48 are now under consideration. Claims 13-22, 36 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 12-27-2002, paper No. 24, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-12, 23-27, 33-35, 37-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules encoding a fusion polypeptide comprising a catalytic domain of any glycosyltransferase and a catalytic domain of any accessory enzyme that catalyzes the formation of the nucleotide sugar.

The specification does not contain any disclosure of the structure of the DNA sequences that are encompassed by the claims. The genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of encoding many proteins with

different structures. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification does not disclose even a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicants have traversed the above rejection arguing they were the first to discover the use of fusion of a glycosyltransferase and an accessory enzyme and that Examiner is referring to the *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) and that they disagree with Examiner's rejection. Applicants, in summary, argue that at the time of application the structure of polynucleotides encoding many glycosyltransferases including sialyltransferases from both prokaryotic and eukaryotic sources were well known to those skilled in the art. Therefore, applicants argue, for known DNA sequences a reference to a public sequence disclosure is sufficiently descriptive and that information that is well known in the art need not be described in detail in the specification. Applicants argue that those of skill in the art recognize how to access the structure of the isolated DNA sequences and how to manipulate those sequences. Examiner respectfully disagrees with such an argument as being persuasive to overcome the rejection. This is because, even though the art may provide the description of several known glycosyltransferases and accessory enzymes, it does not provide the same for those that are being discovered or will be discovered at a later time. However, applicants claims continue to read on those sequences that are still being discovered irrespective of the fact whether they can be used in the making of a fusion protein.

Furthermore, applicants claim read on polynucleotides encoding fusion proteins that can be used for any process.

In response to Examiner's allegation in the previous rejection, that applicants do not provide adequate written description even for a representative number of the species claimed i.e., both structure and function of the polynucleotides, applicants respond that they have provided both structural description and functional description. Applicants argue that application contains numerous references to sequences of glycosyltransferase and of accessory enzymes and that these references provide the required structural disclosure. Examiner respectfully disagrees with such an argument and reiterates that mere recitation of references which disclose other glycosyltransferases and accessory enzymes does not satisfy written description requirements. By structure, Examiner means the nucleotide sequence information by way of providing SEQ ID NO. Next applicants argue that information about enzymatic activity of the fusion proteins is providing "relevant identifying characteristics". Examiner again respectfully disagrees with such a conclusion. Mere stating the enzymatic activity is not considered as relevant identifying characteristics. Identifying characteristics include the source of the DNA/polypeptide, molecular size, and in the case of protein, its molecular weight, pH and temperature optimum etc. Moreover, Examiner has not rejected the claims as lacking description of function of the polynucleotide, and therefore applicants arguments concerning providing functional characteristics as ample written description is moot.

In conclusion, Examiner reiterates that in order to satisfy, written description requirements, applicants must provide both the structure and function of the polynucleotides. While applicants have provided the functional part of the polynucleotide and the encoded polypeptides, they have failed to provide ample structural description. Applicants argument that they have satisfied written description requirements by providing examples of Neisseria CMP-Neu5Ac synthetase and Neisseria α 2,3-sialyltransferase is not sufficient to satisfy written

description requirements. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus or without disclosing any species. In the instant case the claimed genera of includes species which are widely variant in structure. The genus of polynucleotides claimed is structurally diverse as it encompasses polynucleotides encoding all or any glycosyltransferases and all or any accessory enzymes. As such, the description of just the function of the polynucleotides claimed is not sufficient to be representative or sufficient to be fully compliant with written description requirements. Therefore the above rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-12, 23-27, 33-35, is rejected under 35 U.S.C. 103(a) as being unpatentable over Bulow et al. (TIBtech, 1991, Vol. 9:226-231), Defrees et al. (WO 96/32491), and the common knowledge in the art of molecular biology provided by Sambrook et al. (Molecular Cloning, A Laboratory Manual, 2nd Ed, ColdSpring Harbor Laboratory Press, 1989, pages 7.37-7.52).

Claim 1-3, 5-12, 23-27, 33-35 in this instant application are drawn to a polynucleotide encoding a fusion protein comprising a glycosyltransferase such as α 2,3-sialyltransferase and an accessory enzyme such as sialic acid synthetase linked through a peptide linker, wherein the enzymes comprise the signal sequence and a molecular tag (such as for example His tag), expression vector comprising such a polynucleotide, host cells transformed with such vectors and a method of producing the fusion protein by culturing the host cells followed by purifying the fusion protein by permeabilizing the host cell.

Bulow et al. teach the value of multienzyme systems obtained by gene fusion. The reference teaches that preparation of bi and polyfunctional enzymes by gene fusion has a great potential in enzyme technology as they facilitate easy purification and exhibit favorable enzyme kinetics. The reference also teaches that selective enzymes can be made as fusion enzymes and used in biochemical analysis, enzyme process technology and metabolic engineering. However the reference does not teach specifically the making of a fusion polynucleotide encoding a fusion protein comprising a sialyltransferase and sialic acid synthetase.

Defrees et al. teach the enzymatic synthesis of glycosidic compounds such as sialic acid compounds using individual enzymes such as a glycosyltransferase, a sialyltransferase and a

CMP-NeuAc synthetase for generation of sialic acid and CTP (see entire document and specifically claims 1-10). The reference teaches in detail the other requirements for the enzymatic synthesis of carbohydrate compounds involving multiple enzymes. However, while the reference teaches the use of each individual enzymes isolated by recombinant or natural sources the reference does not teach the use of gene fusion either for making these multiple enzymes.

Sambrook et al. provide an exhaustive volume of methods that can be used for various gene manipulations including making fusion polynucleotides, introduction of linker sequences and use of tag sequences in recombinant proteins for easy purification. The reference also teaches purification of recombinant proteins using the molecular tags associated with such proteins. Techniques such as permeabilizing cells for easy access of the encoded enzymes to the substrates are also well k known in the art.

Combining the teachings of all the three above references it would have been obvious to one of ordinary skill in the art to make a bifunctional fusion polynucleotide (as taught by Bulow et al.) encoding sialyltransferase and sialic acid synthetase taught by Defrees et al. using the methods taught by Sambrook et al. one of ordinary skill in the art would be able to take the polynucleotides encoding the sialyltransferase and the sialic acid synthetase taught by Defrees et al. required for regeneration of CMP-NANA in the enzymatic process and make a single fusion polynucleotide linked through a peptide linkage and having the signal sequence and tag sequence using the techniques and methods provided by Sambrook et al. One of ordinary skill in the art would have been motivated to do so as Bulow et al. teach that bi-functional enzymes can be made by gene fusion and such fusion proteins can be used in process technology. As Defrees et

al. teach that there is a desire to make carbohydrate structures such as sialic acid which has an important role in pharmaceutical industry and synthesizing some carbohydrate structures are expensive due to unavailability of pure enzymes in sufficient quantities, one of ordinary skill in the art would have been motivated to make a fusion polynucleotide encoding a sialyltransferase and a sialic acid synthetase. One of ordinary skill in the art would have a reasonable expectation of success since Bulow et al. teach bi-functional fusion proteins encoded by fusion polynucleotides and provide few examples of the same, Defrees et al. teach a process involving the above two enzymes and Sambrook et al. provide techniques that have been used successfully by a number of inventors over a long period of time.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

Claims 37-48 rejected under 35 U.S.C. 103(a) as being unpatentable over Bulow et al., Defrees et al., and Sambrook et al. as applied to claims 1-3, 5-12, 23-27, 33-35 above, and further in view of Gilbert(a) et al. (Eur. J. Biochem., 1997, Vol. 187:187-194) and Gilbert(b) et al. (Biotech. Lett., 1997, Vol. 19(5):417-420). Claims 37-48 are drawn to an polynucleotide encoding a fusion polypeptide comprising a bacterial, a Neisserial α 2,3-sialyltransferase and CMP-Neu5Ac synthetase, comprising a signal sequence and a molecular tag wherein the two polypeptides are linked through a peptide linker, an expression vector comprising said polynucleotide, a host cell expressing said vector, a method of making said polypeptide by growing the host cells and followed by purification of the fusion polypeptide and permeabilizing the host cell.

The references of Bulow et al., Defrees et al., and Sambrook et al. as applied to claims 1-3, 5-12, 23-27, 33-35 has already been discussed above.

Gilbert(a) et al. teach the characterization of a recombinant *Neisseria* α 2,3-sialyltransferase which plays an important role transfer of sialic acid from CMP-NANA to acceptor oligosaccharides which in turn play a role in cell-cell recognition. The reference also teaches that investigation of the enzymology of glycosyltransferase involved in LOS biosynthesis is limited due to the lack of bacterial glycosyltransferase. The reference provides the amino acid sequence of the enzyme from which a cDNA clone can be developed.

Gilbert(b) et al. teach the purification and characterization of the recombinant CMP-sialic acid synthetase (CSA) from Neisseria and teach its use coupled with α 2,3-sialyltransferase(ST) to synthesize CMP-sialic acid which is further attached to various biopolymers. The reference teaches that the major application of the CSA is in coupled reactions with sialyltransferases to sialylated oligosaccharides using CTP and NANA as substrates instead of CMP-Neu5Ac which is relatively unstable and expensive. The reference teaches the use of CSA and ST in a coupled reaction to sialylated FCHASE-lactose. The reference concludes that CSA enzyme works effectively in a coupled reaction with a ST. the reference also lists several advantages of CSA. However, the reference does not teach the use of fusion polynucleotide comprising encoding sequences of both the above enzymes.

Combining the teachings of the above references it would have been obvious to one of ordinary skill in the art to make a single bi-functional fusion enzyme as taught by Bulow et al. using the CSA and SA taught by Gilbert et al. references. One of ordinary skill in the art would have been motivated to do so in order to develop a one-pot synthesis of FCHASE-lactose. One

of ordinary skill in the art would be motivated to make a fusion protein or a host cell comprising a polynucleotide expressing said fusion protein (comprising a Neisseria CSA and ST as taught by Gilbert et al.) because the reference teaches a method involving the use of the two enzymes in the same vessel and that the synthetase works effectively in a coupled reaction with ST. Those skilled in the art would be motivated to permeabilize such host cells using well known methods in the art, so that the enzymes become easily accessible for the acceptor and donor substrates, for direct use of such host cells in sialylating reactions. Furthermore, such a method would obviate the use of expensive and unstable CMP-Neu5Ac from an external source as it is generated *in situ* and used immediately in the sialylation step. One of ordinary skill in the art would have a reasonable expectation of success since the Gilbert references teach both the enzymes and their compatibility in synthesizing FCHASE-lactose, Bulow et al. teach the increasing use of bi-functional enzymes and Sambrook et al. teach methods for developing fusion protein encoding polynucleotide and methods of making recombinant protein.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Double Patenting

Claims 1-3, 5-12, 23-27, 33-35, of this application conflict with claims 1-3, 5-6, 8-12, 23-27, 33-35 of Application No. 10/317,723. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-3, 5-12, 23-27, 33-35, provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim1-3, 5-6, 8-12, 23-27, 33-35 of copending Application No. 10/317,773. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

MANJUNATH RAO
PATENT EXAMINER

Manjunath N. Rao Ph.D.
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10/1/03